31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Detecting Complexity Abnormalities in Dyslexia Measuring Approximate Entropy of Electroencephalographic Signals

Ioannis I. Andreadis, Giorgos A. Giannakakis, Charalabos Papageorgiou, and Konstantina S. Nikita, *Senior Member, IEEE*

Abstract— **Dyslexia constitutes a specific reading disability, a condition characterized by severe difficulty in the mastery of reading despite normal intelligence or adequate education. Electroencephalogram (EEG) signal may be able to play an important role in the diagnosis of dyslexia. The Approximate Entropy (ApEn) is a recently formulated statistical parameter used to quantify the regularity of a time series data of physiological signals. In this paper, we initially estimated the ApEn values in signals recorded from controls subjects and dyslectic children. These values were firstly used for the statistical analysis of the two groups and secondly as feature input in a classification scheme. We also used the cross-ApEn methodology to get a measure of the asynchrony of the signals recorded from different electrodes. This preliminary study provides promising results towards correct identification of dyslexic cases, analyzing the corresponding EEG signals.**

I. Introduction

THE human brain function is determined by activation and interaction mechanisms of the millions of neurons from which it is constituted. Their oscillatory activity is increasingly thought to get synchronized during physiological or pathological brain states, at stimulation or during the performance of certain tasks (e.g. sleep-wake states, increased attention tasks, optical stimulation, epileptic seizures, etc.) [1]. Dyslexia constitutes a specific reading disability, a condition characterized by severe difficulty in the mastery of reading despite normal intelligence or adequate education [2]. Electrophysiological studies have shown that there are physiological deficits in dyslectic subjects [3]-[4], which may affect cognitive functions of the brain such as selective attention, working memory, audio or language process.

It is questionable whether the electroencephalogram signal can be used for the purpose of the dyslectic cases detection as dyslexia is probably a condition related to the brain's electrical activity. In order to examine the electrophysiological background of dyslectic condition, we investigate the regularity and the degree of order of the EEG signal. If a stimulus takes place, brain's response activates generators which begin to act together in a coherent way producing the event-related potentials (ERP). This can be thought as the transition of a system from a general disorder to a state of increased order.

In addition, neuronal systems have been shown to exhibit some kind of nonlinear or chaotic behavior, which makes it reasonable to apply methods from the theory of non-linear dynamics, such as the entropy [5], to the EEG signal. Entropy has been applied in many fields of science like information theory, signal analysis and computer science. High entropy values indicate high level of disorder of a system, whereas low values describe a more ordered system capable to produce some work.

Approximate entropy is a statistical parameter proposed by Pincus to quantify the regularity of a time series data of physiological signals [6]. It has already been used in many applications such as analysis of heart rate variability [7]-[10], detection of epilepsy [11]-[12] and analysis of the endocrine hormone release pulsatility [13]. Higher ApEn means wide disorder while lower ApEn means regularity.

ApEn method can be used only for the evaluation of the regularity of a single time series. However, in many applications, a measure of similarity between different time series is needed. To this end, Cross Approximate Entropy (cross-ApEn) can be used, providing a measure of the asynchrony of a pair of signals [14]. The method has already been applied in the field of endocrinology [15]-[16]. As in the case of ApEn, higher cross-ApEn values imply greater degree of asynchrony between the two time-series and reversely.

In the present work, ApEn has been used in order to decide whether an EEG/ERP signal corresponds or not to a dyslectic case. Furthermore, we applied the cross-ApEn method to quantify the degree of asynchrony between EEG signals of the same subject, recorded at different electrodes, in order to perform statistical analysis of the two groups (controls-dyslectics).

II. Materials and Methods

A. Selection of patients and controls

We studied 38 patients (twenty six boys and twelve girls with mean age and standard deviation 11.47±2.12 years) fulfilling the criteria of dyslexia as described in the 10th edition of the International Classification of Diseases (ICD-10). The patients were recruited from the Department of

Manuscript received June 18, 2009.

I. I. Andreadis, G. A. Giannakakis and K. S. Nikita are with the Biomedical Simulations and Imaging Laboratory, National Technical University of Athens, Greece (corresponding author: I. Andreadis, phone: 30-210-7722968; e-mails: iandr@biosim.ntua.gr, ggian@biosim.ntua.gr, knikita@cc.ece.ntua.gr).

C. Papageorgiou is with the University of Athens, Department of Psychiatry, Eginition Hospital, Athens, Greece and University Mental Health Research Institute (UMHRI), Athens, Greece (e-mail: labisp@otenet.gr).

Psychiatry of the Eginition Hospital in Athens, where the EEG was recorded.

The control group consisted of 19 children, including 7 boys and 12 girls with mean age and standard deviation 12.21±2.25 years. The statistical t-test for the mean ages of the two groups did not show any significant differences.

The local ethics committee approved the study. All control subjects and all caregivers of the demented patients gave their informed consent for participation in the current study. An EEG was recorded from all patients and controls. All of them had undergone assessment of educational attainment including reading, comprehension, spelling and arithmetic ability. Participants with hearing difficulties, history of head injury, attention deficit disorders or neurological disease were not included in the study.

B. Data recording and acquisition

The EEGs and ERPs were recorded at the 15 scalp loci of the international 10–20 system (channels Fp1, F3, C5, C3, Fp2, F4, C6, C4, O1, O2, P4, P3, Pz, Cz, Fz), with all electrodes referenced to the chin. An electrode placed on the subject's forehead served as ground. With the subjects in a relaxed state, awake and with closed eyes so as to minimize eye movements, data were recorded from each subject. Eye movements were recorded through electro-oculogram (EOG) and recordings with EOG higher than 75 μV were rejected. EEG data were first sampled at frequency of 1 kHz so that for signals in the frequency range 0–35 Hz the Shannon theorem is over satisfied. For each trial of the experiment, rest EEG signal was recorded for 500 msec before the stimulus and ERP was recorded for 1000 msec after the stimulus onset. A single sound tone of either high (3000 Hz) or low frequency (500 Hz) was presented to the subjects through earphones, followed by numbers which had to be memorized. Noise was considered to be a random process with zero man value. For this reason, the signal's SNR (ERP in relation to rest EEG) was improved by averaging across the 52 trials of the experiment.

C. Approximate Entropy

ApEn was introduced as a quantification of regularity in sequences and time series data, initially motivated by applications to relatively short, noisy data sets [6]. Approximate entropy returns a non-negative single value reflecting the predictability of future values in a time series on the basis of previous values, with larger values corresponding to more complexity or irregularity in the data. Given N data points from a time series *{x(n)}={x(1), x(2),., x(N)}*, the ApEn value is calculated through the following steps:

1. We form the vector sequences *X(1), X(2),…, X(N-m+1)*, defined by *X(i)=(x(i), x(i+1)…, x(i+m-1))*, which represent m consecutive values, commencing with the ith point.

2. We estimate the distance between X(i) and X(j), defined by

$$d[X(i), X(j)] = \max_{1\le k\le m}\{|x(i+k-1) - x(j+k-1)|\} \quad (1)$$

3. For each X(i) we estimate the number $N_i^m(r)$ of vectors such that

$$d[X(i), X(j)] \le r \quad (2)$$

with r representing the noise filter level.

Then, we estimate the parameters C_i^m as,

$$C_i^m(r) = \frac{N_i^m(r)}{N-m+1} \quad (3)$$

4. We define $\varphi^m(r)$ as the mean value of the parameters C_i^m:

$$\phi^m(r) = \frac{\sum_{i=1}^{N=m+1} \ln C_i^m(r)}{N-m+1} \quad (4)$$

5. ApEn(m,r,N) is calculated using $\varphi^m(r)$ and $\varphi^{m+1}(r)$ as follows:

$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \quad (5)$$

Briefly, ApEn measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width) on subsequent incremental comparisons. Comparisons between time series segments can only be made with the same values of m and r.

D. Cross Approximate Entropy

Cross Approximate Entropy (Cross-ApEn) is a two parameter family of statistics introduced as a measure of asynchrony between two paired time series [14]. Cross-ApEn can be employed to compare sequences from two distinct yet intertwined variables in a network, herein applied to the EEG signals as recorded from different electrodes.

Given two N-length paired time series u and v, cross-ApEn(m,r,N) measures, within tolerance r, the (conditional) regularity or frequency of v-patterns similar to a given u-pattern of window length m. Larger cross-ApEn values indicate greater signal asynchrony. The precise mathematical definition is thematically similar to that for ApEn:

1. We form the vector sequences *x(i)=(u(i), u(i+1),..., u(i+m-1))* and *y(j)=(v(j), v(j+1),..., v(j+m-1))* which represent m consecutive values, commencing with the i_{th} and j_{th} point, respectively.

2. We define the distance between x(i) and y(j), defined as

$$d[x(i), y(j)] = \max_{1\le k\le m}\{|x(i+k-1) - y(j+k-1)|\} \quad (6)$$

3. For each x(i) we compute the number $N_i^m(r)$ of vectors such that

$$d[x(i), y(j)] \le r \quad (7)$$

We compute then the parameters C_i^m defined as

$$C_i^m(r)(v \,||\, u) = \frac{N_i^m(r)}{N-m+1} \quad (8)$$

4. We define $\phi^m(r)$ as the mean value of the parameters C:

$$\phi^m(r)(v \,||\, u) = \frac{\sum_{i=1}^{N=m+1} \ln C_i^m(r)(v \,||\, u)}{N-m+1} \quad (9)$$

5. Cross-ApEn(m,r,N) is calculated as:

$$crossApEn(m,r,N)(v \,||\, u) = \phi^m(r)(v \,||\, u) - \phi^{m+1}(r)(v \,||\, u) \quad (10)$$

Typically, Cross-ApEn is applied to normalized {u*(i), v*(i)} time series, where u*(i) = [u(i)−mean(u)]/s.d.(u) and v*(i) = [v(i)−mean(v)]/s.d.(v) (s.d. is the standard deviation). We should also note here that there is a direction dependence, and as a result $\phi^m(r)(v \,||\, u)$ will not be generally equal to $\phi^m(r)(u \,||\, v)$.

III. RESULTS

ApEn and Cross-ApEn were estimated for 15 channels (Fp1, F3, C5, C3, Fp2, F4, C6, C4, O1, O2, P4, P3, Pz, Cz, Fz and T6) with m=2 and r=0.2 of each waveform data. Each signal was preprocessed by subtracting its mean value and dividing by its standard deviation (s.d.) providing normalized waveforms. The results were averaged between groups (controls, dyslectics) within the EEG/ERP waveforms (1500 samples). The average ApEn values (mean ± s.d.) for the controls and dyslexics are shown in Table 1. It can be observed that there are three electrodes (C5, O2, P4) that appear to discriminate significantly the two groups.

Then, we evaluated the ability of ApEn to discriminate dyslectics from control subjects at the statistically significant electrodes. We constructed a classifier based on the Support Vector Machines (SVM) methodology [17]. We trained the classifier with a dataset constituted from the ApEn values of the significant electrodes for all 57 subjects, control and dyslectics. To this end, the library LIBSVM [18] was used in our experiments. Due to the limited size of the available dataset, we used the Leave One Out technique which is mainly used in such situations because of its good generalization ability.

To evaluate the classifier, we measured both the sensitivity and specificity achieved. Sensitivity is the percentage of dyslectics correctly recognized by the classifier, whereas specificity represents the percentage of control subjects classified correctly by the classifier, using the ApEn values from the statistically significant electrodes. Finally, accuracy is a related measure that quantifies the number of subjects (dyslectics and control subjects) accurately classified. The results are presented in Table 2. We observe that a satisfactory value of sensitivity is achieved, which is encouraging as it indicates that dyslexia may be identified through the analysis of the EEG signal using the ApEn parameter. The results achieved at the end of this process are comparable with those reported on previous studies [19]-[20].

TABLE I
THE AVERAGE APEN VALUES (MEAN ± S.D.) OF THE EEG/ERP SIGNAL FOR THE CONTROLS AND DYSLECTICS

Electrode	Controls	Dyslectics	p-value
Fp1	0,095 ± 0.056	0,104 ± 0.097	0,6953
F3	0,112 ± 0.046	0,105 ± 0.034	0,4806
C5	0,141 ± 0.054	0,114 ± 0.027	**0.014***
C3	0,128 ± 0.043	0,122 ± 0.039	0,6026
Fp2	0,096 ± 0.052	0,096 ± 0.045	0,9463
F4	0,123 ± 0.056	0,113 ± 0.065	0,5713
C6	0,127 ± 0.048	0,114 ± 0.036	0,2473
C4	0,123 ± 0.054	0,114 ± 0.038	0,4808
O1	0,140 ± 0.082	0,112 ± 0.066	0,1688
O2	0,164 ± 0.079	0,123 ± 0.059	**0.0299***
P4	0,148 ± 0.056	0,121 ± 0.042	**0.0453***
P3	0,141 ± 0.060	0,126 ± 0.039	0,2557
Pz	0,143 ± 0.056	0,128 ± 0.043	0,2586
Cz	0,114 ± 0.043	0,106 ± 0.025	0,359
Fz	0,111 ± 0.052	0,094 ± 0.032	0,1377

TABLE II
SYSTEMS' PERFORMANCE MEASURES

	Performance Measures		
	Sensitivity	***Specificity***	***Accuracy***
SVM classification scheme	89.47%	57.89%	78.95%

At the next step, Cross-ApEn values were calculated for each pair of electrodes. As the Cross-$ApEn_{ij}$ is different than Cross-$ApEn_{ji}$ of *i,j* electrodes, a total number of 15*(15-1)=210 Cross-ApEn values were calculated for each subject. It was tested that data follow normal distribution. To this end, our goal was to investigate whether there are statistically significant pairs of electrodes. These results may give us important information on possible connections between different compartments in the brain. The cross-ApEn values can also be used as input in a new classification scheme for discrimination between dyslectic and controls. Due to the great number of statistically significant pairs, further analysis is needed in order to combine the values of the two methodologies in a unified classification scheme.

Fig. 1 indicates the p-values of equality test between controls and dyslectics groups (two tailed t-test).

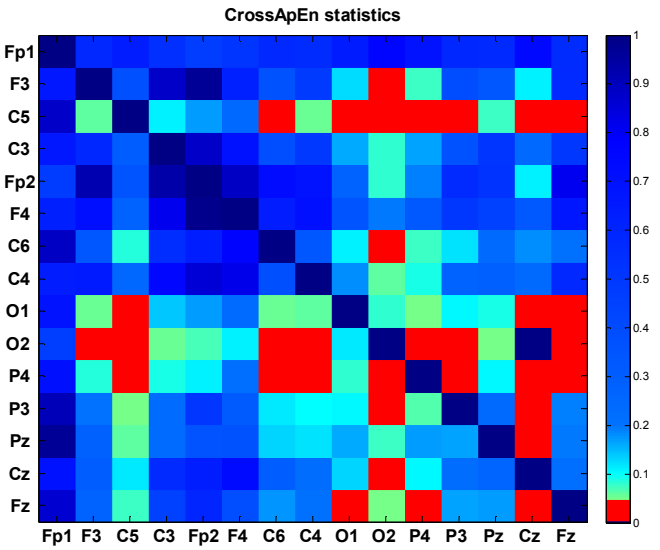

Fig.1. Differentiation results between controls and dyslectics for all pairs of electrodes (colorbar indicates p-values)

IV. DISCUSSION

In this study, the application of nonlinear analysis methods ApEn and Cross-ApEn on EEG and ERP signals was investigated. Our study involved 19 controls and 38 dyslectic children whose EEG and ERP signals were recorded at 15 electrodes according to 10-20 system. It was found that there are some specific electrodes (C5, O2, P4) that could discriminate statistically the average ApEn values of the two groups with dyslectics having lower mean values as compared to controls.

An SVM classification scheme has been implemented in order to classify the cases, using the ApEn values as estimated at the statistically significant electrodes. The results are encouraging, indicating that the analysis of the EEG signal may reveal valuable information for the identification of dyslexia. The sensitivity achieved is 89.47%, whereas specificity is equal to 57.89%.

Using Cross-ApEn which is a measure of irregularity between two time series, it was found that electrodes C5, Cz, C4, P4, O2 show differences between controls and dyslectics. Although Cross-ApEn appears to provide higher discrimination ability, there is still no clear pattern and further analysis is needed to interpret the results.

V. CONCLUSIONS

The application of methods able to measure the different degree of complexity of the signals recorded appears to provide useful tools for the discrimination of dyslexic and control subjects.

Although ApEn and Cross ApEn cannot yet be applied as diagnostic tools, they can provide useful information about signals' properties that remains hidden when classical and conventional statistical methods are used. These preliminary results could be proven quite helpful in the understanding of deeper mechanisms of neurological/ neuropsychological disorders. Our future goals include methodology refinement which aims at the improvement of the classification results and at a complete framework for the diagnosis and identification of dyslexia, based on the EEG signal's analysis.

REFERENCES

[1] O. A. Rosso, S. Blanco, J. Yordanova, V. Kolev, A. Figliola, M. Schurmann, and E. Basar, "Wavelet entropy: a new tool for analysis of short duration brain electrical signals," J. Neurosci. Methods, vol. 105 (1),pp. 65-75, Jan. 2001.

[2] E. Grikorenko, "Developmental Dyslexia: An Update of Genes, Brains and Enviroment", J. Child. Psychol. Psychiat., vol. 42, no. 1, pp. 91 – 125, 2001.

[3] M. L. Bonte, L. Blomert, "Developmental dyslexia: ERP correlates of anomalous phonological processing during spoken word recognition," Brain Res Cogn Brain Res, vol. 21, issue 3, pp. 360-376, 2004.

[4] V. Csepe, D. Szucs, F. Honbolygo, "Number-word reading as challenging task in dyslexia? An ERP study," International Journal of Psychophysiology, vol. 51, issue 1, pp. 69-83, December 2003.

[5] B. Berthold. Entropy. Best Practice & Research Clinical Anaesthesiology, Vol. 20, No. 1, pp. 101–109, 2006.

[6] S. Pincus "Approximate entropy as a measure of system complexity". Proc. Nati. Acad. Sci. USA, Vol. 88, pp. 2297-2301, March 1991.

[7] S. M. Pincus, T. R. Cummins, and G. G. Haddad,"Heart rate control in normal and aborted SIDS infants," Amer. J. Physiol., vol. 264, no. 3, pp. R638–R646, 1993.

[8] S. M. Pincus and A. L. Goldberger, "Physiological time series analysis: what does regularity quantify?," Amer. J. Physiol., vol. 266, pp. H1643– Hl656, 1994.

[9] J. S. Richman and J. R. Moorman,"Physiological time-series analysis using approximate entropy and sample entropy," Amer. J. Physiol., vol. 278, pp. H2039–H2049, 2000.

[10] W. S. Kim, Y. Z. Yoon, J. H. Bae, and K. S. Soh, "Nonlinear characteristics of heart rate time series: Influence of three recumbent positions in patients with mild or severe coronary artery disease," Physiol. Meas., vol. 26, pp. 517–529, 2005.

[11] V. Srinivasan, C. Eswaran, N. Sriraam. Approximate Entropy-Based Epileptic EEG Detection Using Artificial Neural Networks. Biomedicine, Vol. 11, No. 3, May 2007.

[12] Ocak, H., Automatic detection of epileptic seizures in EEG using discrete wavelet transform and approximate entropy, Expert Systems with Applications, 2008, doi:10.1016/j.eswa.2007.12.065.

[13] S.M. Pincus,"Older males secrete luteinizing hormone and testosterone more irregularly and joint more asynchronously, than younger males," Proc. Natl. Acad. Sci. U.S.A., vol. 93, pp. 14100–14105, 1996.

[14] S.M. Pincus, B.H. Singer , "Randomness and degrees of irregularity". Proc Natl Acad Sciences USA. 93:2083–2088, 1996.

[15] F. Roelfsema , S. Pincus , J. Veldhuis , "Patients with Cushing's Disease Secrete Adrenocorticotropin and Cortisol Jointly More Asynchronously than Healthy Subjects." Journal of Clinical Endocrinology and Metabolism Printed in U.S.A., Vol 83, No2, 1998.

[16] S.M. Pincus, T. Mulligan , A. Iranmanesh ,S. Gheorghiu , M. Godschalk, J.D.Veldhuis, "Older males secrete luteinizing hormone (LH) and testosterone more irregularly, and jointly more asynchronously, than younger males". Proc Natl Acad Sci USA. 93:14100 –14105.1996.

[17] C. J. C. Burges, "A Tutorial on Support Vector Machines for Pattern Recognition," Knowledge Discovery Data Mining, 2:1-43, 1998.

[18] Chih-Chung Chang and Chih-Jen Lin, LIBSVM: a library for support vector machines, 2001. Software available at http://www.csie.ntu.edu.tw/~cjlin/libsvm.

[19] D.L. Molfese, "Predicting Dyslexia at 8 Years of Age Using Neonatal Brain Responses". Brain and Language 72,pp. 238–245, 2000.

[20] F.H. Duffy, M.B. Denckla, P.H. Bartels, G. Sandini, L.S. Kiessling, "Dyslexia: Automated diagnosis by computerized classification of brain electrical activity". Annals of Neurology 7, pp. 421-428, 1980.